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Implementation Of Intervention Program For Controlling Glucose Level Among ICU Patients

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Abstract

Introduction: Hyperglycemia and insulin resistance are common in critically ill patients, even if they have not previously had diabetes, and the risk of mortality or significant morbidity is high among those who are treated in the intensive care unit (ICU) for more than 5 days.

Study objectives: To assess the effect of glucose management protocol on mortality and morbidity in a heterogeneous population of critically ill adult patients.

Methods and materials:

Study design: A randomized controlled trial.

Study setting: Intensive care unit (ICU) for adult patients at King Hussein Medical Center, the Royal Medical Services.

Study sample: A total of 50 patients were included in this study and assigned randomly into two groups, control group (N=25), and intervention group (N=25).

Study protocol: The intervention group subjects were to undergo a glucose control protocol with insulin infusion titrated to maintain blood glucose level in a target range of 120-160 mg/dL; except septic patients, in whom the target was higher, 160- 180 mg/dL. Patients in the second group (control

group) were treated by a conventional approach with reduction of blood glucose level only if the level was markedly elevated (>200 mg/dL) to maintain blood glucose level in a target range of 180-200 mg/dL

Study findings: Although the difference in mortality between the two treatment groups was not significant at 28 days (p=0.370) and at 60 days (p=0.555), but it was to be considered for further improvements. No significant increase in hypoglycemia episodes was reported in our blood glucose level target. There was no significant difference in the development of new organ failure, new renal insufficiency, number of patients undergoing transfusion of packed red blood cells, use of antibiotics for more than 10 days, length of stay in the ICU and length of stay in the hospital. It was noticed that the rates of positive blood cultures were lower in the interventional group (8%) than in the control group (32), (p=0.068).

Conclusion: The glucose management protocol resulted in significantly improved glycemic control and was not associated with increased rate of death or hypoglycemia.

Keywords: Intensive care unit (ICU), hypoglycemia, intervention, control, randomized controlled trial

Introduction

Patients in the intensive care unit (ICU) are predisposed to elevated blood glucose levels because of common clinical interventions, such as the use of corticosteroids, vasopressors, glucose-containing intravenous fluids used for drug or fluid administration, enteral or parenteral nutrition, and dialysis (Krinsley, 2005).

Hyperglycemia adverse clinical outcomes

Extensive observational data have shown a consistent, almost linear relationship between high blood glucose levels in hospitalized patients and adverse clinical outcomes, even in patients without established diabetes (Krinsley *et al*., 2003).

Hyperglycemia has been identified as an independent risk factor for adverse outcome in numerous clinical settings at admission or throughout hospitalization. It predisposes patients to many of the typical ICU complications such as severe infections, sepsis, excessive inflammation, critical illness polyneuropathy, ICU prolonged intensive care dependence, prolonged need of mechanical ventilation multiple organ failure and excessive mortality (Vanhorebeek *et al*., 2007).

Neurology

Poor glycemic control, though even mildly elevated glucose levels, is associated with increased morbidity and mortality in critically ill brain injury and trauma patients; this is more pronounced in nondiabetic patients (Gale *et al*., 2007). Hyperglycemia has been reported to augment ischemic brain injury and worsen outcomes in many animal and human studies. One study evaluated 267 non-diabetic patients with non-penetrating head injuries. Among patients with more severe head injury, BG levels >200 mg/dL were associated with worse outcomes (Rovlias and Kotsou, 2000). Apart from the predictive value of hyperglycemia for mortality of patients with severe brain injury, a significant relationship was found between high blood glucose levels and worse neurologic status, impaired pupil reactivity, intracranial hypertension, and longer hospital length of stay (Bochicchio *et al*., 2005; Laird *et al*., 2004).

Similarly, hyperglycemia predicted a higher risk of death after stroke and a poor functional recovery in those patients who survived. Elevated brain glucose concentrations resulting from hyperglycemia, in conjunction with an ischemia-induced shift to anaerobic glycolysis, led to more severe elevations of brain lactic acid concentrations and more profound acidosis (Gale *et al*., 2007).

In patients with acute ischemic stroke, negative neurologic outcomes associated with hyperglycemia include the evolution of hypoperfused tissue, greater infarct size, worse functional outcome, longer hospital stays, and higher hospital charges (Bruno *et al*., 2002). Hyperglycemia is also independently associated with increased mortality at 30 days, one year, and 6 years after stroke. And when hyperglycemia is present before an ischemic or anoxic event, neurologic damage is worse (Parsons *et al*., 2002).

Infections

Increasing evidence suggests that hyperglycemia impedes normal physiologic responses to infection and is statistically related to distinct changes of humoral and cellular immune functions (Wasmuth *et al*., 2004). High glucose levels negatively affect polymorphonuclear neutrophil function and intracellular bactericidal opsonic activity and causes apoptosis in proximal tubular epithelial cells (Allen *et al*., 2003).

Postoperative infections

In vitro and in vivo studies report substantial impairment in immune function and wound healing associated with hyperglycemia (Weekers *et al*., 2003). Mechanisms include complement inactivation, irregularities in granulocyte adherence, impaired phagocytosis, delayed chemotaxis and

oxidative burst, and decreased bactericidal activity. Collagen deposition is impaired, possibly due to decreased fibroblast proliferation.

The degree of leukocyte abnormalities varies directly with BG concentrations; impaired phagocytic function occurs with BG levels as low as 200 mg/dL. Nonenzymatic glycosylation of immunoglobulins - which causes their inactivation – also contributes to the risk of infection (Lewis *et al*., 2004).

A prospective cohort study assessed the correlation between preoperative glucose control and the subsequent risk of infectious complications in 411 diabetic patients who were undergoing coronary artery surgery. After adjusting for confounding variables, patients with mean BG concentrations more than 200 mg/dL following the surgery had higher rates of leg and chest wound infections, pneumonia, and urinary tract infections and mortality rates (Hill-Golden *et al*., 1999).

Septic patients

The available literature suggests a causal link between hyperglycemia and adverse outcome in sepsis. In addition, a strong link has been described between increased blood glucose levels and the risk of critical illness polyneuropathy in sepsis and the systemic inflammatory response syndrome. Most deaths in the ICU occurring beyond the first few days of critical illness are attributable to non-resolving failure of multiple organ systems, either due to or coinciding with sepsis (Vanhorebeek *et al*., 2007).

Mortality

Kosiborod *et al (*2005) found a relation between high admission glucose and increased mortality in elderly patients hospitalized with acute myocardial infarction (Kosiborod *et al*., 2005). A retrospective study was conducted on all injured patients admitted to the surgical ICU for more than 48 hours. Non-survivors had higher average glucose than survivors ($p<0.03$). In ICU the mortality rate for newly hyperglycemic patients approached one in three (Umpierrez *et al*., 2002). A retrospective analysis of a heterogeneous population of critically ill patients revealed that even a modest degree of hyperglycemia was associated with increased hospital mortality (Krinsley *et al*., 2003).

Controlling hyperglycemia in ICU patients

Although extensive research efforts during the last decade focused on strategies to prevent or reverse the potentially lethal multiple organ failure, only few of them revealed positive results. One of these strategies is blood glucose control with insulin (Berghe., 2004). Another way for controlling

hyperglycemia is by controlling the exogenous nutritional inputs (Chase *et al*., 2006).

Mechanisms of blood glucose control with insulin therapy in the ICU

Several mechanisms are involved and interrelated in explaining the clinical benefits of normoglycemic control; including metabolic and non-metabolic insulin effects, anti-inflammatory effects, prevention of glucose toxicity, and other direct insulin actions on several cell and organ systems. The relative contribution of those different mechanisms, however, is presently unknown (Derde *et al*., 2009).

Lowering blood glucose levels

Critically ill patients suffer from both hepatic and skeletal muscle insulin resistance. The increased metabolic insulin signal was observed in postmortem skeletal muscle, but not in liver biopsies of insulin-treated patients. This suggests that in critically ill patients exogenous insulin does not affect hepatic insulin resistance and lowers blood glucose levels mainly through stimulation of skeletal muscle glucose uptake (Langouche *et al*., 2007). Insulin therapy also attenuated the cortisol (counterregulatory hormone) response to critical illness, without involvement of altered cortisol-binding activity, also suppress indirectly the synthesis and production of TNF and IL-2 which play a role in increased gluconeogenesis (Vanhorebeek *et al*., 2006).

Study objectives

The main objective of the current study is to evaluate the impact of the blood glucose level control on the morbidity and mortality of intensive care unit patients.

Materials and Methods

Study design

A randomized, controlled trial of blood glucose management which involved adult medical and surgical ICU patients, who received treatment in the ICU for 3 or more consecutive days, at King Hussein Medical Center, and the Royal Medical Services.

Study population

Adults, who were expected to require treatment in the medical and surgical ICU for 3 or more consecutive days, and within 24 hours after admission to an intensive care unit, were eligible for the study.

Inclusion criteria

Patients were eligible to participate in this study if they satisfied the following criteria:

• Patients, who were expected to require treatment in the ICU for 3 or more consecutive days after admission, the decision was made by the treating ICU specialist.

• Patients who had an arterial line or central line in situ or the placement of the lines was imminent as part of routine ICU management.

• Need for insulin therapy.

• Informed consent was approved by the patient or his/her legal surrogate.

Exclusion criteria

Patients were not included if:

• Age is less than 18 years.

• Imminent death (cardiac standstill or brain death anticipated in less than 24 hours and the treating clinicians were not committed to full supportive care.

• Patients who were admitted to the ICU for treatment of diabetic ketoacidosis or for hyperosmolar state.

• Patients who were expected to be eating before the end of the day following the day of admission to the ICU.

• Patients who had previously suffered hypoglycemia without a documented full neurological recovery.

• Patients who were considered at abnormally high risk of suffering hypoglycemia (e.g. known insulin secreting tumor or history of unexplained or recurrent hypoglycemia or fulminant hepatic failure).

• Patients who had previously been enrolled in the study.

• Patients who cannot provide prior informed consent and there is documented evidence that the patient has no legal surrogate.

• Patients who had been in the study ICU for more than 24 hours during this admission.

• Patients who were transferred from other hospitals (another ICU) and who had been in the ICU for more than 24 hours.

Sample size

A sample was randomly selected, daily odd or even hidden numbered papers were picked up randomly to include eligible patients for the study, odd numbers were chosen for the interventions and even ones were chosen for the controls. Patients sample size was 50 patients.

Statistical Analysis

SAS, version 9.1, was used for statistical analysis. Clinical data were expressed as mean, median and as percentages. *P* values less than 0.05 were considered significant. For univariate analysis of end points Chi-square test or Fisher's exact test. Continuous variables were compared with the use of unpaired t-test, or Wilcoxon rank-sum test.

Results

Outcomes and adverse events.

Twenty eight days after randomization, (28%) of patients died in the intervention group, as compared to (42%) in the control group (Table 5). The difference in mortality between the two treatment groups was not significant after adjustment for the predefined baseline risk factors (p= 0.370).

Sixty days after randomization, (32%) of patients died in the intervention group compared to (40%) in the control group. The difference in mortality between the two treatment groups was not significant (p= 0.555). Place of death was mainly in the ICU. There was no significant difference between the two groups in the average median of length of stay in the ICU (p= 0.596) or stay in the hospital (p= 0.380).

The numbers of patients in whom new single or multiple organ failures developed were similar between the intervention and the control groups (p=0.142).

There were no significant differences between the two groups in the percentage of mechanical ventilation (p=0.135), number of days on mechanical ventilation (p=0.945) and percentage of patients who needed renal-replacement therapy (p= 0.139).

There were no significant differences between the two groups in the percentage of patients who received blood transfusion (p= 0.136), in the mean number of units of blood transfused (p=0.576), or in the percentage of patients using antibiotics for more than 10 days (p=0.141). The rate of positive blood cultures was lower in the intervention group than in the control group (8% and 32% respectively, p=0.068).

Severe hypoglycemia (defined as a blood glucose level 45 mg/dL) was not observed in patients of either groups, and study treatment was not discontinued prematurely because no serious adverse events were noticed.

The recorded number of episodes of hypoglycemia was 2 in the intervention group, as compared to zero episodes in the control group (p=0.148); as confirmed by a laboratory measurement. The time spent in the hypoglycemic range was negligible (less than 2 hours), and resulted in rescue dextrose administration.

Secondary subgroup analysis for the primary outcome were based on an unadjusted test of interaction in a logistic regression model , with the

strata used for randomization (type of admission) as covariates, as well as age, gender, diabetes, location before ICU admission, and use of mechanical ventilation at baseline, septic shock and trauma.

A significant association was observed with the type of admission for death at 28 days with higher mortality rate for medical ICU than surgical ICU (p=0.015), and at 60 days it was still significant (p=0.032).

No association was observed between diabetic and non -diabetic patients for death. The time from randomization to death in the two treatment groups was not significantly different compared with the use of the log-rank test, and the results are presented as Kaplan–Meier curves and are shown in figure 1.

Table 1: Outcomes and Adverse Events associated with study protocol

Outcome measure	Intervention group	Control group	*P*-value
Death, (%) At day 60 At day 28	32 % 28%	40% 40%	0.555 0.370
Hypoglycemia, (%)	8%	0%	0.148
Days in the ICU, median (minimum-maximum)	5 (3-33)	6 (3-34)	0.596
Days in the hospital, median (minimum-maximum)	3 (0-22)	3 (0-14)	0.380
Mechanical ventilation, (%)	92%	84%	0.135
Days on mechanical ventilation, median (minimum-maximum)	4 (2-20)	5 (2-25)	0.945
Renal replacement therapy, (%)	8%	12%	0. 139
No. of new organ failures, (%) 0 1 2 3 and more	 64% 24% 8% 4%	 56% 20% 24% 0%	0.142
Blood culture positive for pathogenic organisms, (%)	8%	36%	0.068
Use of antibiotics for more than 10 days, (%)	40%	44%	0.141
Transfusion of packed red cells, (%)	68%	84%	0.136
No. of units of packed cells transfused, mean ±SD	2.56 ± 1.95	2.24 ± 2.067	0.576

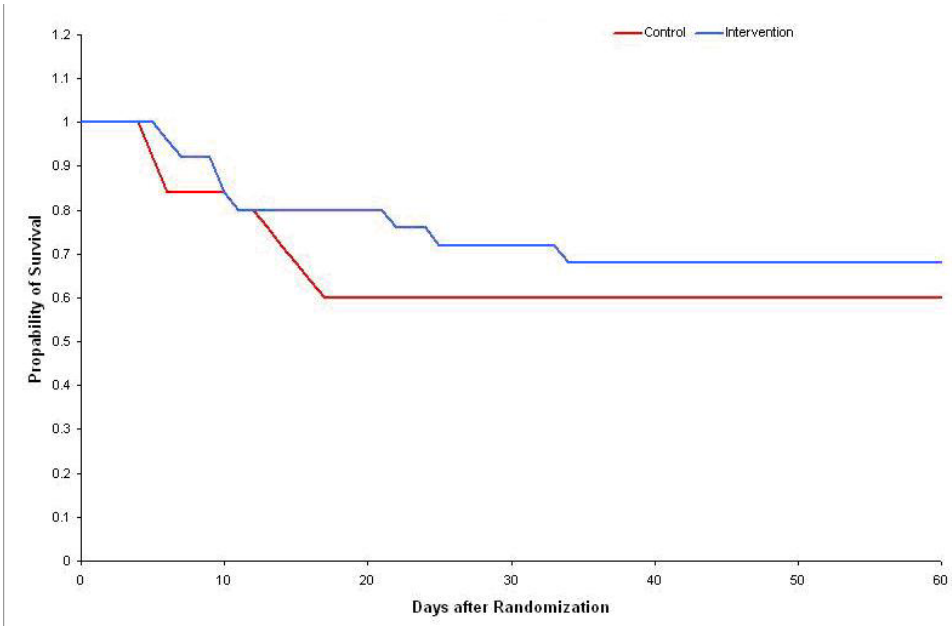

Figure 1: Kaplan–Meier curves of probability of survival at 28 days and 60 days

Discussion

In this randomized controlled trial involving adults in the mixed ICU, we found that a new target of blood glucose control that was used in the intervention group, as compared with a conventional glucose control in the control group, did not increase the absolute risk of death at 28 days and at 60 days.

The difference in mortality remained not significant after adjustment for potential confounders at 28 days (p=0.370), and at 60 days (p=0.555), between two groups in our study. This finding agrees with the result of a meta-analysis stating that the different targets ofintensive insulin therapy (glucose level [6.1 mmol/L versus [8.3 mmol/L) did not influence either mortality (Fahey *et al*., 2009).

It was noticed by secondary subgroup analysis for the primary outcome that the percentage of death was significantly higher in medical ICU patients than surgical ICU patients (p= 0.015), indicating that surgical patients may benefit more from insulin treatment. As found in previous studies (Van den Berghe *et al*., 2001, He *et al*., 2007) and a meta-analysis (Donald *et al*., 2009). There was no significant difference in other secondary outcomes between the two groups; in the median length of stay in the ICU or in the hospital, the need for mechanical ventilation and renal-replacement therapy, the need for blood transfusion and new organ failures that developed during admission.

In our study the rate of positive blood cultures was lower in the intervention group than that in the control group; (8% and 32% respectively) (p=0.068), which reflects reduction in the risk of septicemia. In this randomized controlled trial involving adults in the mixed ICU we found that a new target of blood glucose control that was used in the intervention group, as compared with a conventional glucose control in the control group, did not increase the absolute risk of death at 28 days and at 60 days.

The difference in mortality remained not significant after adjustment for potential confounders at 28 days (p=0.370), and at 60 days (p=0.555), between two groups in our study. This finding agrees with the result of a meta-analysis stating that the different targets of intensive insulin therapy (glucose level [6.1 mmol/L versus [8.3 mmol/L) did not influence either mortality (Fahey *et al*., 2009).

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In our study the rate of positive blood cultures was lower in the intervention group than that in the control group; (8% and 32% respectively) (p=0.068), which reflects reduction in the risk of septicemia. This finding was reported previously by other studies (Van den Berghe, *et al*., 2001; Grey, *et al*., 2004).

There was no significant difference in the percentage of patient to whom antibiotics was used for more than 10 days between the two groups in our study; due to the fact that some patients were inappropriately given antibiotics until the day of discharge in an attempt to prevent infections while they were hospitalized may have led to the use of antibiotics for longer than the recommended period so we could not detect difference.

The basic clinical characteristics of all patients enrolled in our study showed that the mean HbA1C was less than 6.5% indicating that hyperglycemia was not sustained and that both diabetic and non-diabetic patient in the ICU revealed stress induced hyperglycemia.

On the basis of our data, we speculate that a target blood glucose level of less than 160 mg/dL may be adequate. This more relaxed target for

glucose control with a range of 40 mg/dL will be likely associated with less risk of inadvertent hypoglycemia than other suggested targets.

Evidence exists that intensive insulin therapy prevents complications such as severe nosocomial infections, acute renal failure, liver dysfunction, critical illness polyneuropathy, muscle weakness, and anemia, and, thus, reduces the time that patients are dependent on intensive care. The use of insulin therapy to maintain normoglycemia for at least a few days improves survival and reduces morbidity (Vanhorebeek *et al*., 2006).

Conclusion

Hyperglycemia develops commonly in the critically ill and impacts outcome in patients with diabetes but, even more so, in patients with stress-induced hyperglycemia. The data of the present study showed that a blood glucose target of less than 160 mg per deciliter in general, and target of less than 180 for septic patients, did not significantly increase mortality more than a target of less than 200 mg /per deciliter among critically ill adult patients.

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